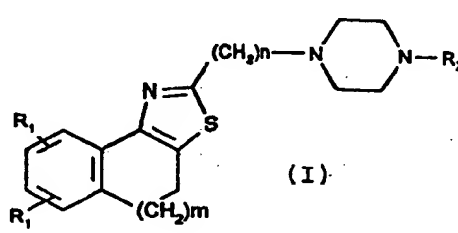


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(54) Title: 1(HETERO)ARYL-4-(CONDENSED THIAZOL-2-YLALKYL)-PIPERAZINE DERIVATIVES, THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF 5-HT _{1A} -RECEPTOR MEDIATED DISORDERS			
(57) Abstract Aryl and heteroaryl piperazine derivatives of formula (I) wherein, R ₁ is hydrogen, halogen, trifluoromethyl, C ₁ -C ₆ alkyl, C ₁ -C ₆ alkoxy, C ₁ -C ₆ alkylthio, hydroxy or C ₁ -C ₆ mono- or di- alkylamino; m is zero or an integer from 1 to 3; n is an integer from 1 to 5; and R ₂ is an aryl or a heteroaryl group optionally substituted by one or more substituents selected from halogen, trifluoromethyl, cyano, C ₁ -C ₃ alkoxy and C ₁ -C ₃ alkylthio; and their pharmaceutically acceptable salts are useful in the treatment of disorders depending on serotonin action at the level of 5-HT _{1A} receptor sites. A process for preparing compounds of formula (I) and pharmaceutical compositions comprising them are also described.			
		 <p>(I)</p>	

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1-(HETERO)ARYL-4-(CONDENSED THIAZOL-2-YLALKYL)-PIPERAZINE DERIVATIVES,
THEIR PREPARATION AND THEIR USE IN THE TREATMENT OF 5-HT_{1A}-RECEPTOR
MEDIATED DISORDERS

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The present invention relates to aryl and heteroaryl piperazine derivatives, to a process for their preparation and to pharmaceutical compositions comprising them. These compounds possess central serotonergic activity and can be useful in the treatment of central nervous system disorders.

Serotonin (5-hydroxytryptamine, 5-HT) is a biogenic amine which was first discovered in the gut. 5-HT was later shown to correspond to a vasotonic substance found in the serum and was therefore called serotonin. Serotonin is also found in the brain and is involved in a wide range of behaviours such as sleep, appetite, pain perception, locomotion, thermoregulation and sexual activity.

Furthermore, serotonergic drugs are used in the treatment of a number of pathological states such as migraine, depression and anxiety.

The multiple actions of serotonin are mediated by the specific interaction of this amine with several receptors. Pharmacological and physiological studies identified distinct receptors which were designated 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT₂, 5-HT₃ and 5-HT₄ (Med. Chem. Res., 1994, 4, 16-84).

It is known that the 5-HT_{1A} receptor sub-family seems to be important for many functions in humans. For instance, altered functions of this receptor sub-family is involved in the genesis of a number of pathological conditions such as, e.g., anxiety, depression, psychosis, abnormality of sleep and feeding, organic mental diseases and alteration of the blood pressure.

Therefore, pharmaceutical compounds able to act on 5-HT_{1A} receptor sites may be useful in the treatment of disorders

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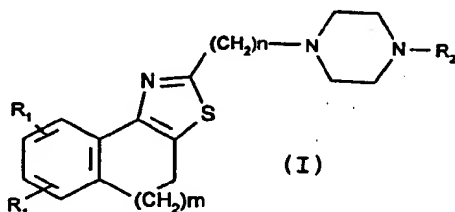
which depend on serotonin action at the level of 5HT_{1A} receptors.

Perrone et al. disclosed in "Il Farmaco 50(2) 77-82, 1995", N-methyl-N-tricyclic naphtho-[1,2-d]thiazol piperazine derivatives, which were found to possess 5-HT₃ receptor binding affinity whereas they displayed no affinity versus D₂, 5-HT₁ and 5-HT₂ receptors.

In view of the above results, a person skilled in the art, seeking to prepare compounds which possess 5-HT_{1A} receptor affinity, would be taught away from considering tricyclic naphtho-[1,2-d]thiazol-piperazine structures.

It has now surprisingly been found that N-aryl and heteroaryl-piperazin-naphtho[1,2-d]thiazol derivatives, which show a remarkable structural similarity with the above compounds disclosed by Perrone, exhibit a noticeable degree of affinity towards 5-HT_{1A} receptor sites.

Accordingly, the present invention provides an aryl or heteroaryl piperazine derivative of formula (I)



wherein

R₁ is hydrogen, halogen, trifluoromethyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy or C₁-C₆ mono-or di-

alkylamino;

m is zero or an integer from 1 to 3;

n is an integer from 1 to 5;

R₂ is an aryl or a heteroaryl group optionally substituted

5 by one or more substituents selected from halogen,
trifluoromethyl, cyano, C₁-C₃ alkoxy and C₁-C₃ alkylthio;

and the pharmaceutically acceptable salts thereof.

In the present specification the hydrocarbon chain of the
alkyl, alkoxy, alkylthio and alkylamino groups may be a linear
10 or branched chain.

A C₁-C₆ alkyl group may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl or n-pentyl; preferably it is methyl or ethyl.

15 Preferably a C₁-C₆ alkoxy group is a C₁-C₃ alkoxy group, in particular methoxy or ethoxy.

Preferably a C₁-C₆ alkylthio group is C₁-C₃ alkylthio group, in particular methylthio or ethylthio.

20 Preferably a C₁-C₆ mono- or di-alkylamino group is a C₁-C₃ di-alkylamino group, in particular dimethylamino or diethylamino.

Preferably m is zero 1 or 2.

Preferably n is an integer from 1 to 4.

An optionally substituted aryl group may be, for example, an optionally substituted phenyl ring; preferably it is an
25 unsubstituted phenyl ring or a phenyl ring substituted by one substituent selected from halogen, trifluoromethyl, cyano, C₁-C₃ alkoxy and C₁-C₃ alkylthio; more preferably it is an unsubstituted phenyl ring or a phenyl ring substituted by a C₁-C₃ alkoxy group.

An optionally substituted heteroaryl group is an optionally substituted 5- or 6- membered heteromonocyclic ring which comprises one or more heteroatoms selected from N, O and S; preferably it is a 5- or 6-membered unsubstituted heteromonocyclic ring containing one or two heteroatoms selected from nitrogen and sulphur such as, e.g., pyrazole, thiazole, thiophene, pyridine, pyrimidine, pyrazine or pyridazine; more preferably it is a 6-membered unsubstituted heteromonocyclic ring containing one or two nitrogen atoms such as, e.g., a pyridyl, a pyrazinyl or a pyrimidinyl residue.

As mentioned above the present invention includes aryl and heteroaryl piperazine derivatives in the form of pharmaceutically acceptable salts.

Pharmaceutically acceptable salts according to the invention are the salts with pharmaceutically acceptable acids, both inorganic such as, e.g., hydrochloric, nitric, sulfuric or phosphoric, and organic acid such as, e.g., maleic, fumaric, tartaric, methanesulphonic, glutamic or malic acid.

Preferred salts according to the invention are hydrochlorides.

Preferred compounds of the invention are compounds of formula (I) wherein

R_1 is hydrogen or a C_1 - C_6 alkoxy group;

m is zero 1 or 2;

n is an integer from 1 to 4;

R_2 is an unsubstituted phenyl ring, a phenyl ring substituted by a C_1 - C_3 alkoxy group, an unsubstituted pyridyl ring, an unsubstituted pyrimidinyl ring or an unsubstituted pyrazinyl ring;

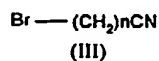
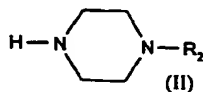
and the pharmaceutically acceptable salts thereof.

Examples of specific compounds of the invention are the following:

(1) 6-Methoxy-2-{4-(4-(2-methoxy-phenyl)-piperazin-1-yl)-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;

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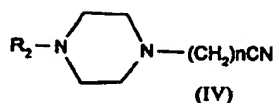
- (2) 2-[(4-phenyl-piperazin-1-yl)-methyl]-4,5 dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (3) 2-[2-(4-phenyl-piperazin-1-yl-ethyl)-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- 5 (4) 2-[3-(4-phenyl-piperazin-1-yl)-propyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (5) 2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (6) 7-Methoxy-2-{3-[4-(2-methoxy-phenyl)-piperazin-1-yl]-propyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- 10 (7) 7-Methoxy-2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (8) 7-Methoxy-2-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (9) 7-Methoxy-2-{4-[4-(2-pyridyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- 15 (10) 6-Methoxy-2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (11) 5-Methoxy-2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- 20 (12) 5-Methoxy-2-{4-[4-(2-pyridyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride; and
- (13) 5-Methoxy-2-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride.
- 25 The compounds of the invention can be obtained by a process comprising:
- a) condensing a compound of formula (II) with a compound of formula (III)



wherein

n is an integer from 1 to 5 and

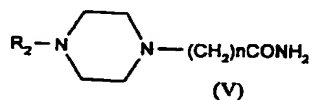
5 R_2 is an aryl or a heteroaryl group unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, cyano, C_1-C_3 alkoxy and C_1-C_3 alkylthio, so obtaining a compound of formula (IV)



10

wherein n and R_2 are as defined above;

b) hydrolysing the compound of formula (IV) under acid conditions to obtain a compound of formula (V)

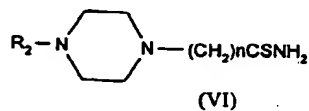


15

wherein n and R_2 are as defined above;

c) reacting the compound of formula (V) with P_2S_5 or the Lawesson reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide], to obtain a compound of formula (VI)

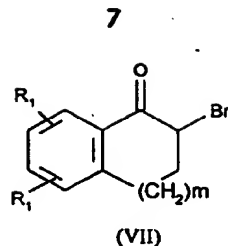
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25

wherein R_2 and n are as defined above;

d) condensing the compound of formula (VI) with a compound of formula (VII)



wherein R_1 is hydrogen, halogen, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy or C_1-C_6 mono- or di-alkylamino and m is zero or an integer from 1 to 3; and, if desired, converting the resulting compounds of formula (I) into another compound of formula (I); and/or if desired converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

10 The condensation described as step a) may be carried out, for example, by reaction of a compound of formula (II) with a compound of formula (III) in a solvent such as, e.g., dimethylformamide (DMF) or tetrahydrofuran about 30° to about 75°C .

15 The hydrolysis described as step b), which is performed as a controlled acid hydrolysis, may be carried out, for example, by pouring a compound of formula (IV) into ice cooled concentrated sulfuric acid for a time varying from about 25 to about 50 minutes.

20 The reaction described as step c) may be carried out, for example, by heating a compound of formula (V) with the Lawesson reagent in toluene at reflux for a time varying from about 3 to about 7 hours, or treating a compound of formula (V) with P_2S_5 in pyridine at reflux for a time varying from about 4 to about 8 hours.

25 The condensation described as step d) may be carried out, for example, by reacting a compound of formula (VI) with a compound of formula (VII) in a suitable solvent such as, e.g., THF, ethanol, diethyl ether or dioxane, at a temperature ranging from about 35°C to about 110°C .

The optional conversion of a compound of formula (I) into a salt thereof may be carried out, for example, by adding a stoichiometric amount of a suitable pharmaceutically acceptable acid dissolved in a suitable solvent such as, e.g., diethyl ether, ethanol or methanol, to a solution of the base. The salt can be recovered by concentration of the solution.

The compounds of the present invention possess high affinity towards 5-HT_{1A} receptor sites having agonist or antagonist activity at central level.

They are therefore useful in the treatment of disorders which depend on serotonin action at the level of 5HT_{1A} receptor sites. For example, they can be useful in the treatment of anxiety, depression, schizophrenia, pain (Drug of the future, 1988, 13(5), 429-437), age associated memory impairment, Alzheimer's disease, feeding and sexual disorders.

By virtue of their neuroprotective activity, the compounds of the present invention may also be useful to alleviate neuronal damage following cerebral ischemia (Stroke, 1990, 21(4), 161-167).

A human or animal body may thus be treated by a method which comprises the administration thereto of a pharmaceutically effective amount of a compound of formula (I) or salt thereof. The condition of the human or animal can thereby be improved.

The affinity of the compounds of the present invention towards 5-HT_{1A} receptor sites can be assessed by evaluating the binding profile of the compounds of formula (I).

As an example, a representative number of compounds of formula (I), namely compounds (1) to (13) listed above, were tested according to the method reported in Journal of Neurochemistry, 44, 1685, (1985), and Molecular Pharmacology, 21, 301, (1981).

The obtained results are reported in Table 1 below.

Table 1

Compound	α_1	α_2	D ₁	D ₂	5-HT _{1A}	5-HT ₂
(1)	0.052	0.092	0.59	0.02	0.0032	0.25
(2)	0.13	0.3	9.15	0.12	0.042	0.3
(3)	0.11	0.16	2.69	0.21	0.17	0.063
(4)	0.12	0.11	2.00	0.076	0.069	0.28
(5)	0.17	0.26	2.02	0.22	0.067	0.066
(6)	0.09	0.16	1.86	0.11	0.034	0.17
(7)	0.049	0.5	1.18	0.025	0.012	0.87
(8)	0.2	0.38	1.61	0.15	0.007	0.72
(9)	0.058	0.02	0.43	0.011	0.0041	0.055
(10)	1.14	3.77	>10	0.68	0.4	3.18
(11)	0.052	0.018	1.77	0.024	0.01	0.066
(12)	0.19	0.39	1.49	0.061	0.0082	0.082
(13)	0.035	0.046	0.66	0.008	0.0037	0.24

Affinity is expressed as IC₅₀ μ M.

The tabulated data clearly demonstrate the high affinity of the compounds of formula (I) towards 5HT_{1A} receptor sites.

A mammal, e.g. a human or animal, may thus be treated by a method which comprises administering thereto a pharmaceutically effective amount of a compound of formula (I) as defined above.

The compounds of the invention can be administered in a variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally, in the form of suppositories; parenterally, e.g. intramuscularly, or by intravenous injection or infusion; topically, e.g. in the form of creams. Preferably they are administered by oral or parenteral route, more preferably by oral route.

The dosage depends on the age, weight, conditions of the patient and administration route. For example, a suitable dosage for oral administration to adult humans may be from 1mg to 1000mg per kg per day, preferably from 50mg to 500mg per kg.

The present invention also provides pharmaceutical compositions comprising, as an active ingredient, a compound of formula (I) as defined above or a pharmaceutically acceptable salt thereof, in mixture with a pharmaceutically acceptable excipient (which can be diluent and/or carrier).

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a pharmaceutically suitable form.

For example, the solid oral forms may contain, together with the active compound, diluents, e.g., lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. a starch, alginic acid, alginates or sodium starch glycolate; effervescing

mixtures; dyestuffs; sweeteners; wetting agents such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be
5 manufactured in known manner, for example, by means of mixing granulating, tableting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be, e.g. syrups, emulsions and suspension.

10 The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol; in particular a syrup to be administered to diabetic patients can contain as carriers only products not metabolizable to glucose, or metabolizable in very small amount to glucose, for example
15 sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar sodium alginate, pectin pectin, methylcellulose, caroxymethylcellulose, or polyvinyl alcohol.

20 The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycol, e.g. propylene glycol and if desired, a suitable amount of lidocaine hydrochloride.

25 The solutions for intravenous injections or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The suppositories may contain together with the active compound
30 a pharmaceutically acceptable carrier, e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

Conventional carriers may be used for topical formulations.

The following examples, representative of the compounds of the invention, illustrate but do not limit the invention.

The number into bracket reported before the chemical name of the compounds prepared according to the following examples, corresponds to the preferred compounds listed on pages 5 and 6 of the present specification.

Example 1

(1) 6-Methoxy-2-{4-(4-(2-methoxy-phenyl)-piperazin-1-yl)-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

A stirred suspension of 1.92 g of 1-(2-methoxy-phenyl)piperazine and 2.16 g of 5-bromopentane nitrile and 1.4 g of potassium carbonate in 50 ml of acetonitrile was refluxed for 1 hour.

After cooling, the solvent was removed and the residue taken up in ethyl acetate was washed with brine.

After drying, the crude reaction mixture was chromatographed on silica gel eluting with ethyl acetate/dichloromethane 7/3, affording 2.6 g of 1-(4-cyanobutyl)-4-(2-methoxy-phenyl)piperazine in 94.3% yield as a oil.

To a stirred solution of 10 ml of concentrated sulfuric acid was slowly added 2.75 g of 1-(4-cyanobutyl)-4-(2-methoxy-phenyl)piperazine and the resulting mixture was stirred first at 50°C for 30' then set aside at room temperature for 1 hour.

The reaction mixture was poured on ice, and after alkalization with concentrated ammonia solution, was extracted several times with dichloromethane.

After drying, the solvent was removed and the residue crystallized from diethyl ether affording 2.46 g of 1-(4-aminocarbonylbutyl)-4-(2-methoxy-phenyl)piperazine in 84% yield as white solid.

13

To a refluxing solution of 2.93 g of 1-(4-aminocarbonylbutyl)-4-(2-methoxy-phenyl)piperazine in 30 ml of anhydrous toluene was added portionwise 4.1 g of Lawesson's reagent.

After heating for 2 hours, the cold solution was filtered and
5 washed 3 times with 1 M hydrochloric acid solution.

The acid extracts were basified with concentrate ammonia solution then extracted with ethyl acetate.

After drying, the crude mixture was chromatographed on silica gel eluting with chloroform/methanol 95/5 affording 1.85 g of 1-
10 (4-aminothiocarbonylbutyl)-4-(2-methoxy-phenyl)piperazine in 65% yield.

A stirred solution of 3.2 g of 1-(4-aminothiocarbonylbutyl)-4-(2-methoxy-phenyl)piperazine and 3.82 g of 2-bromo-7-methoxy-1-tetralone- in 50 ml of diethyl ether was refluxed overnight.

15 After cooling, the solution was extracted several times with 1 M hydrochloric acid solution.

The acid phase was basified, extracted with ethyl acetate and dried.

The solvent was removed and the residue chromatographed on
20 silica gel eluting with chloroform/methanol 98/2 affording 2.9 of the title compound in 65% yield. This by action of 1 M hydrochloric acid in methanol was converted in the corresponding hydrochloride, m.p. 223-225°C.

25 Example 2

(2) 2-[(4-phenyl-piperazin-1-yl)-methyl]-4,5 dihydro-naphtho[1,2-d]thiazole hydrochloride

Operating as in Example 1 but employing bromoacetonitrile
30 instead of 5-bromopentane nitrile and 1-phenylpiperazine instead of 1-(2-methoxy-phenyl)piperazine and 2-bromo-1-tetralone instead of 2-bromo-6-methoxy-1-tetralone, the title compound was obtained in 78% yield, m. p. 208-210°C.

Example 3

(3) 2-[2-(4-phenyl-piperazin-1-yl-ethyl)-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

5

Operating as in Example 2 but employing 2-bromopropane nitrile instead of bromoacetonitrile, the title compound was obtained in 56% yield, m.p.177-178°C.

10 Example 4

(4) 2-[3-(4-phenyl-piperazin-1-yl)-propyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

Operating as in Example 2 but employing 3-bromobutyro-nitrile instead of bromoacetonitrile, the title compound was obtained in 47% yield, m.p.205-206°C.

Example 5

(5) 2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

20

Operating as in Example 2 but employing 4-bromovalero-nitrile instead of bromoacetonitrile, the title compound was obtained in 64% yield, m.p.208-210°C.

25 Example 6

(6) 7-Methoxy-2-{3-[4-(2-methoxy-phenyl)-piperazin-1-yl]-propyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

Operating as in Example 1 but employing 4-bromobutyro-nitrile instead of 5-bromovalero-nitrile and 1-phenylpiperazine instead of 1-(2-methoxy-phenyl)piperazine and 2-bromo-5-methoxy-1-tetralone instead of 2-bromo-6-methoxy-1-tetralone, the title compound was obtained in 34% yield, m. p.199-201°C.

30

Example 7

(7) 7-Methoxy-2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

5

Operating as in Example 6 but employing 5-bromovalero-nitrile instead of 4-bromobutyro-nitrile, the title compound was obtained in 43% yield, m.p.200-202°C.

10 Example 8

(8) 7-Methoxy-2-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

Operating as in Example 7 but employing 1-(2-methoxy-phenyl)piperazine instead of 1-phenylpiperazine, the title compound was obtained in 37% yield, m.p.201-203°C.

15

Example 9

(9) 7-Methoxy-2-{4-[4-(2-pyridyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

20

Operating as in Example 7 but employing 1-(2-pyridyl)piperazine instead of 1-phenylpiperazine, the title compound was obtained in 48% yield, m.p.245-247°C.

25 Example 10

(10) 6-Methoxy-2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

Operating as in Example 1 but employing 1-phenylpiperazine instead of 1-(2-methoxy-phenyl)piperazine, the title compound was obtained in 47% yield, m.p.221-222°C.

30

Example 11

(11) 5-Methoxy-2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

- 5 Operating as in Example 10 but employing 2-bromo-7-methoxy-1-tetralone instead of 2-bromo-6-methoxy-1-tetralone, the title compound was obtained in 35% yield, m.p.195-197°C.

Example 12

- 10 (12) 5-Methoxy-2-{4-[4-(2-pyridyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

Operating as in Example 11 but employing 1-(2-pyridyl)piperazine instead of 1-phenylpiperazine, the title compound was obtained
15 in 45% yield, m.p.219-221°C.

Example 13

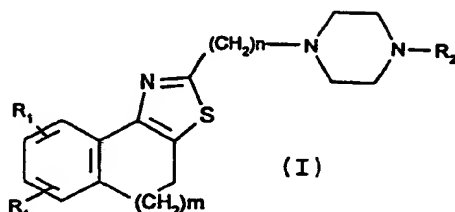
- (13) 5-Methoxy-2-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride

20

Operating as in Example 11 but employing 1-(2-methoxy-phenyl)piperazine instead of 1-phenylpiperazine, the title compound was obtained in 32% yield, m.p.207-209°C.

CLAIMS

1. An aryl or heteroaryl piperazine derivative of formula (I)



5

wherein

R_1 is hydrogen, halogen, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, hydroxy or C_1 - C_6 mono- or di-alkylamino;

10 m is zero or an integer from 1 to 3;

n is an integer from 1 to 5; and

R_2 is an aryl or a heteroaryl group optionally substituted by one or more substituents selected from halogen, trifluoromethyl, cyano, C_1 - C_3 alkoxy and C_1 - C_3 alkylthio; or a
15 pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein

R_1 is hydrogen or a C_1 - C_6 alkoxy group;

m is zero 1 or 2;

n is an integer from 1 to 4;

20 R_2 is an unsubstituted phenyl ring, a phenyl ring substituted by a C_1 - C_3 alkoxy group, an unsubstituted pyridyl ring, an unsubstituted pyrimidinyl ring or an unsubstituted pyrazinyl ring.

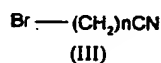
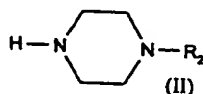
3. A compound as claimed in claim 1 or 2, which is a
25 hydrochloride salt.

4. A compound selected from the group consisting of:

(1) 6-Methoxy-2-{4-(4-(2-methoxy-phenyl)-piperazin-1-yl)-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;

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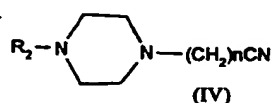
- (2) 2-[(4-phenyl-piperazin-1-yl)-methyl]-4,5 dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (3) 2-[2-(4-phenyl-piperazin-1-yl-ethyl)-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- 5 (4) 2-[3-(4-phenyl-piperazin-1-yl)-propyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (5) 2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (6) 7-Methoxy-2-{3-[4-(2-methoxy-phenyl)-piperazin-1-yl]-propyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- 10 (7) 7-Methoxy-2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (8) 7-Methoxy-2-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (9) 7-Methoxy-2-{4-[4-(2-pyridyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- 15 (10) 6-Methoxy-2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- (11) 5-Methoxy-2-[4-(4-phenyl-piperazin-1-yl)-butyl]-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride;
- 20 (12) 5-Methoxy-2-{4-[4-(2-pyridyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride; and
- (13) 5-Methoxy-2-{4-[4-(2-methoxy-phenyl)-piperazin-1-yl]-butyl}-4,5-dihydro-naphtho[1,2-d]thiazole hydrochloride.
- 25 5. A process for preparing a compound as defined in claim 1, which process comprises:
- a) condensing a compound of formula (II) with a compound of formula (III)



wherein

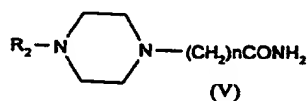
n is an integer from 1 to 5 and

R₂ is an aryl or a heteroaryl group unsubstituted or substituted by one or more substituents selected from halogen, trifluoromethyl, cyano, C₁-C₃ alkoxy and C₁-C₃ alkylthio, so obtaining a compound of formula (IV)



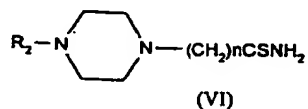
wherein n and R₂ are as defined above;

- b) hydrolysing the compound of formula (IV) under acid conditions so as to obtain a compound of formula (V)



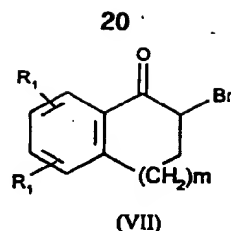
wherein n and R₂ are as defined above;

- c) reacting the compound of formula (V) with P₂S₅ or the Lawesson reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide], to obtain a compound of formula (VI)



wherein R₂ and n are as defined above;

- d) condensing the compound of formula (VI) with a compound of formula (VII)



- wherein R_1 is hydrogen, halogen, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy or C_1-C_6 mono- or di-alkylamino, and m is zero or an integer from 1 to 3; and, if desired, converting the resulting compound of formula (I) into another compound of formula (I); and/or if desired converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.
6. A pharmaceutical composition which comprises, as an active ingredient, a compound as defined in claim 1 in admixture with a pharmaceutically acceptable diluent and/or carrier.
7. A compound as defined in claim 1, for use in the treatment of a disorder depending on serotonin action at the level of 5-HT_{1A} receptor sites.
8. A compound as defined in claim 1, for use in the treatment of anxiety, depression, schizophrenia, pain, age associated memory impairment, Alzheimer's disease, a feeding or a sexual disorder.
9. A compound as defined in claim 1, for use in alleviating neuronal damage following cerebral ischemia.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/03240

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/84 C07D417/12 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	EP,A,0 279 598 (PFIZER INC.) 24 August 1988 see the whole document ---	1-9
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

8 November 1996

Date of mailing of the international search report

26. 11. 96

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INTERNATIONAL SEARCH REPORT

International Application No
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International Application No
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